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Research Article

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The Choleretic Effect of Iodipamide

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ABSTRACT It is well established that a number of organic anions are excreted by the liver into bile in association with a marked increase in bile flow. Previous studies have shown that iodipamide (3,3′-(adipoyldiimino)bis[2,4,6-triiodobenzoic acid]), the radiographic contrast material used for intravenous cholangiography, is a potent choleretic.

Experiments were performed in unanesthetized dogs to determine if the increased bile flow produced by iodipamide is canalicular or ductular in origin, to quantitate the choleresis associated with iodipamide and taurocholate excretion, and to correlate these findings with the results of in vitro studies in which the osmotic activities of iodipamide and taurocholate in both isotonic saline and bile were determined.

The plasma erythritol clearance increased linearly with the excretion of iodipamide, indicating that iodipamide stimulates canalicular bile flow. The choleretic potency of iodipamide (22 ml/mmol) is approximately 3 times that of taurocholate (7.8 ml/mmol), yet the osmotic activity of iodipamide in bile (1.5 mosmol/mmol) is only twice as great as that of taurocholate in bile (0.8 mosmol/mmol). It therefore appears that, per unit of effective osmotic solute secreted, iodipamide carries more water into the bile canaliculi than does taurocholate.

INTRODUCTION

In the past several years, considerable progress has been made in delineating the mechanism by which bile is formed. It appears that bile flow is the result of osmotic filtration of water secondary to the transport of solutes into bile by the bile canalicular and ductular system (2). The excretion of bile salts and other organic substances across the canaliculus is thought to stimulate bile production (choleresis) as a result of their osmotic activity (3). A so-called bile salt-independent bile fraction of canalicular origin has been identified which is probably dependent on the stimulation of inorganic ion transport across the canalicular membrane (4–6). The choleresis induced by most exogenous organic anions seems to be related to their osmotic activity as they are secreted into bile (7, 8). This osmotic activity in bile is markedly influenced by the ability of the anions to interact with bile salt micelles or to form molecular aggregates themselves (9).

Iodipamide,[1] the only organic anion utilized for intravenous cholangiography in the United States, is a potent choleretic (10). This choleretic effect is of interest not only because study of the mechanism by which it occurs may increase the understanding of bile formation, but also because the choleresis associated with its excretion diminishes its concentration in bile. This imposes an inherent limitation on the maximum concentration of iodine obtainable in bile, and thereby restricts the degree of radiographic opacification achieved during intravenous cholangiography.

To study the mechanism by which iodipamide exerts its choleretic effect, experiments were performed in dogs to quantitate the increase in bile flow associated with the biliary excretion of iodipamide and to determine its effects on canalicular bile flow as reflected by changes in erythritol clearance into bile. The effect of iodipamide on the choleresis associated with bile salt excretion was also examined to determine if iodipamide alters canalicular membrane permeability. In vitro studies were performed to measure the increments in osmotic activity caused by addition of measured amounts of iodipamide and taurocholate to both bile and isotonic saline in order to determine if the increase in bile flow produced by iodipamide can be explained entirely by its osmotic activity in bile.

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[1] Cholografin meglumine, E. R. Squibb & Sons, New York.

METHODS

In vivo experiments. Experiments were performed on three trained, unanesthetized, mongrel dogs weighing 17–30 kg. The dogs were prepared several months earlier by cholecystectomy and insertion of a Thomas cannula into the duodenum opposite the major duodenal papilla (11). Indwelling catheters were placed in both external jugular veins for blood collections and infusions. All dogs were fasted for 24 h and deprived of water for 12 h before the experiments. No dog was studied more often than once per week. For bile collection the Thomas cannula was opened and a number 8 Fr cone-tipped ureteral catheter was inserted through the major papilla and passed approximately 4 cm into the common duct. The dogs were gently restrained by a sling in an upright position on a Pavlov stand. The anticholinergic drug, pipenzolate methylbromide,[2] was administered intravenously to minimize fluctuations in bile flow (0.5 mg/kg initially, followed by 0.1 mg/kg every 20 min thereafter) (12). A constant intravenous infusion of 1.5% sodium taurocholate[3] in distilled water (0.5 μmol/min/kg) was given throughout all of the studies to replace bile salts lost because of interruption of the enterohepatic circulation (13).

Bile was continually diverted throughout each experiment and the flow rate was constantly monitored. When bile flow became constant at the beginning of the experiment (at least 1 h after cannulating the bile duct) blood and bile samples were collected as controls. A priming injection of 2.5 μCi of [^{14}C]erythrito[4] dissolved in 70% ethanol was given, followed by a continuous infusion of 0.025 μCi/min. A 15.3% solution of methylglucamine iodipamide (diluted from a 52% solution) was infused at varying rates.

Two experiments were performed in each of three dogs by infusion of iodipamide in a stepwise fashion at seven rates increasing from 0.33 to 7.33 μmol/min/kg. Bile samples (at least 3 ml) were collected at each infusion rate after bile flow had been stable for at least 30 min. Blood samples were collected at the midpoint of each bile collection period. Iodine and [^{14}C]erythritol concentrations were measured in plasma and bile. In one experiment the osmolality of bile at each infusion rate was determined by vapor pressure osmometry at 37°C.[5] The measurement of osmolality in canine bile by the vapor pressure method has been compared with the osmolality obtained by freezing point depression and there is excellent agreement between the two methods. The freezing point method yields osmolality values which are consistently about 7 mosmol/kg higher than those obtained by the vapor pressure method, but differences in osmolality between different samples are faithfully detected by either method.

Two additional studies were performed by infusion of iodipamide at the relatively low rate of 1.0 μmol/min/kg. When the bile flow became constant the infusion was stopped. Blood and bile samples were collected during the infusion when bile flow was constant and then every 20 min for 3 h after the infusion as the bile flow decreased. Iodine and [^{14}C]erythritol concentrations were measured in plasma and bile.

Since iodipamide is administered as the methylglucamine salt, one additional study on the effect of *N*-methylglucamine alone on bile flow and erythritol clearance was performed. *N*-methylglucamine was infused at a rate of 5.47 μmol/min/kg and blood and bile samples were collected before and after the infusion. [^{14}C]erythritol concentrations in plasma and bile were determined.

To study the effect of iodipamide on the choleresis associated with bile salt excretion, a 1.5% solution of sodium taurocholate in distilled water was infused in a stepwise fashion at four rates increasing from 0.5 to 3.0 μmol/min/kg in each of two dogs. Bile samples (at least 3 ml) were collected at each infusion rate after bile flow had been stable for at least 30 min. The bile salt infusion was then stopped and bile samples were collected every 10 min for 1 h thereafter as bile salt excretion decreased. This procedure was then repeated in a second and third study in both dogs while iodipamide was infused at 1.0 μmol/min/kg in the second study and 3.0 μmol/min/kg in the third study. Iodine and bile salt concentrations were measured in bile.

^{14}C activity in plasma and bile was measured by the liquid scintillation method previously described by Wheeler, Ross, and Bradley, and erythritol clearance was calculated (5). Iodine concentrations in plasma and bile were determined by a modification of the thiosulfate titration method described by Zak and Boyle (14). The bile salt concentration in bile was determined by the hydroxysteroid dehydrogenase method of Talalay as modified by Admirand and Small (15). Additions of iodipamide to bile specimens or to aqueous bile acid standards in concentrations up to 35 μmol/ml (the highest concentration ever achieved in bile) had no effect on the measured bile acid concentration.

In vitro experiments. The osmolality of iodipamide and taurocholate in various solutions was determined by vapor pressure osmometry at 37°C. The solutions were prepared in the following manner:

(*a*) Iodipamide acid[6] was dissolved in both fresh dog bile and isotonic sodium chloride by shaking for 1–3 h, and 2 meq of sodium hydroxide were then added for each milliequivalent of iodipamide so that the final solutions contained 35 μmol/ml of disodium iodipamide. These solutions were then serially diluted with fresh dog bile and isotonic sodium chloride, respectively, so that the final concentrations of disodium iodipamide in the solutions were 0, 5, 15, and 25 μmol/ml. The pH of each of the final solutions ranged from 7.8–8.0, as measured by a Beckman pH meter.[7] The concentration of bile salts in the final solutions of dog bile was 75.5 μmol/ml.

The iodipamide acid employed in the in vitro studies contained no sodium or potassium (determined by flame spectrophotometry) and no chloride (determined by electrometric titration).

(*b*) To measure the osmotic activity of iodipamide in bile containing lower concentrations of bile salts, a solution of dog bile containing 35 μmol/ml of disodium iodipamide (prepared as above) was serially diluted with increasing volume of isotonic sodium chloride also containing 35 μmol/ml of disodium iodipamide, so that the bile salt concentration ranged from 0 to 82.5 μmol/ml. The pH of each of the final solutions was 7.8.

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[2] Piptal, generously supplied by Lakeside Laboratories, Inc., Milwaukee, Wis.

[3] Sigma Chemical Co., St. Louis, Mo.

[4] Amersham/Searle Corp., Arlington Heights, Ill.

[5] Mechrolab, (present manufacturer, Hewlett-Packard, Co., Palo Alto, Calif.).

[6] Generously supplied by E. R. Squibb & Sons, Princeton, N. J.

[7] Beckman Instruments, Inc., Fullerton, Calif.

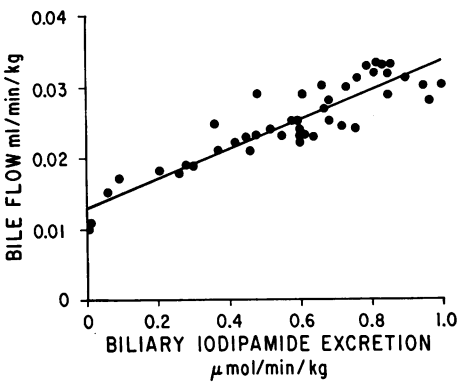

FIGURE 1 The relation between bile flow and biliary iodipamide excretion rate. The data are from two studies in each of three dogs. A line was fitted by the method of least squares to the data (regression equation: $y = 0.0118 + 0.222x$, $r = 0.94$).

(*c*) To measure the osmotic activity of sodium taurocholate in bile, crystalline sodium taurocholate[8] was dissolved in both fresh dog bile and in isotonic sodium chloride by shaking for 30 min so that the final solutions contained approximately 35 μmol/ml of added sodium taurocholate. These solutions were then serially diluted with fresh dog bile and with isotonic sodium chloride, respectively, so that the final solutions contained approximately 0, 5, 15, and 25 μmol/ml of added sodium taurocholate. In these studies the pH of each of the final solutions ranged from 7.9 to 8.0.

The purity of the sodium taurocholate employed in the in vitro studies was confirmed by thin-layer chromatography. However, minor contamination with sodium chloride was detected. The sodium concentration was 1.17 meq/mmol of taurocholate (determined by flame spectrophotometry) and the chloride concentration was 0.17 meq/mmol of taurocholate (determined by electrometric titration). No potassium was detected (determined by flame spectrophotometry).

The concentrations of iodipamide and taurocholate used in the solutions were within the range observed in bile during iodipamide excretion studies in the dog.[9] The iodine concentration in the iodipamide solutions and the bile salt concentration in the bile solutions was determined as described above.

RESULTS

In vivo experiments

There was a linear relationship between the rate of bile flow and the rate of iodipamide excretion in bile (Fig. 1). The biliary excretion of iodipamide ranged from 0 to 1.0 μmol/min/kg as the infusion rate was increased, and the rate of bile flow varied from 0.010 to 0.033 ml/min/kg. Calculation of the slope of the least squares line of the relation between bile flow and iodipamide excretion for all six studies indicates that 22 ml of additional bile are formed for each millimole of iodipamide excreted in the bile.

[8] Chromotographically pure, Calbiochem, San Diego, Calif.

[9] Loeb, P. M., R. N. Berk, G. K. Feld, and H. O. Wheeler. The biliary excretion of iodipamide. Submitted for publication.

Plasma erythritol clearance into the bile was also linearly related to the rate of excretion of iodipamide in bile (Fig. 2). Erythritol clearance increased from 0.013 to 0.045 ml/min/kg as the biliary excretion of iodipamide increased from 0 to 1.0 μmol/min/kg. The slope of the least squares line of this relation indicates that plasma erythritol clearance was increased 24 ml/min for each millimol per minute increment in iodipamide excretion rate. This does not appear to differ from the slope of the least squares line of the relation between bile flow and iodipamide excretion rate.

In two studies in which iodipamide was infused at 1.0 μmol/min/kg until a constant bile flow was observed and then the infusion stopped, the rate of bile flow and erythritol clearance decreased as the biliary excretion rate of iodipamide decreased. The osmolality of bile when measured in one experiment did not change as the bile flow and iodipamide excretion rate increased (Table I). Bile flow and erythritol clearance were not affected by infusion of *N*-methylglucamine alone at a rate of 5.5 μmol/min/kg.

In studies in which bile salt excretion was varied by infusion of sodium taurocholate, the bile flow was linearly related to the excretion rate of bile salts (Fig. 3). In these studies bile salt excretion ranged from 0.06 to 3.20 μmol/min/kg. Lines were fitted by the method of least squares to the data from three studies in each of two dogs. The actual data are not plotted due to the large number of individual data points. Calculation of the slope of the least squares line of the relation between bile flow and bile salt excretion indicates that 7.8 ml of additional bile is formed for each millimole of taurocholate excreted in the bile in the absence of iodipamide infusion, and the positive intercept of bile flow when extrapolated to zero bile salt excretion was

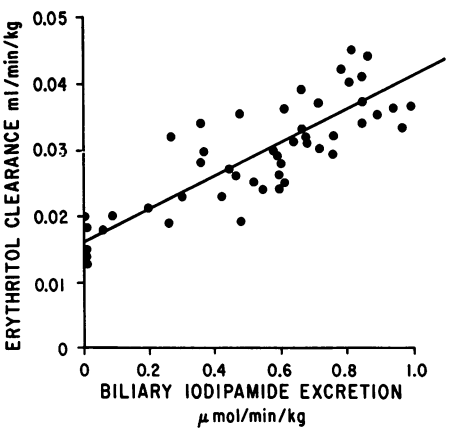

FIGURE 2 The relation between erythritol clearance and biliary iodipamide excretion rate. The data are from two studies in each of three dogs. A line was fitted by the method of least squares to the data (regression equation: $y = 0.0165 + 0.0244x$, $r = 0.83$).

TABLE I
*The Relations Between Iodipamide Excretion Rate, Bile Flow, and Bile Osmolality**

Iodipamide excretion rate	Bile flow	Osmolality
μmol/min/kg	*ml/min/kg*	*mosmol/kg*
0	0.009	273
0.01	0.011	292
0.30	0.019	287
0.60	0.022	291
0.72	0.024	285
0.76	0.024	296
0.60	0.024	290
0.68	0.025	294

* The data are from one experiment in one dog during increasing infusion rates of iodipamide.

0.0025 ml/min/kg. When iodipamide was infused at the rate of 1.0 μmol/min/kg the slope of the least squares line of this relation was approximately the same (7.5), but the positive intercept of bile flow was increased by 0.0075 ml/min/kg from 0.0025 to 0.0100 ml/min/kg. When iodipamide was infused at 3.0 μmol/min/kg the slope of the least squares line was again 7.8, but the positive intercept of bile flow was increased by 0.011 ml/min/kg from 0.0025 to 0.0135 ml/min/kg. Iodipamide excretion in bile was constant throughout each of the studies where iodipamide was infused.

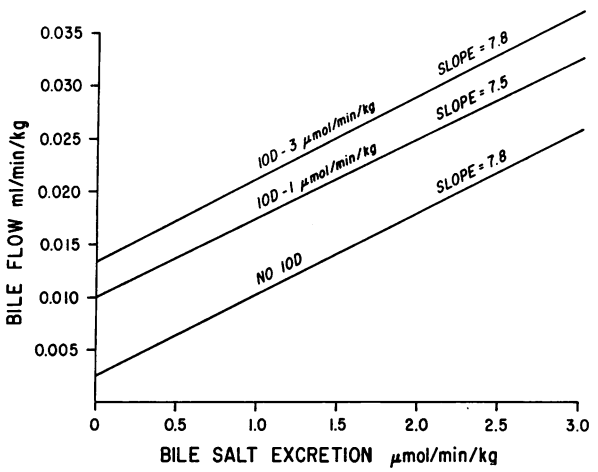

FIGURE 3 The relation between bile flow and bile salt excretion in bile during and in the absence of iodipamide (Iod) infusion. The data are from three studies in each of two dogs. In one study in each of two dogs iodipamide was not infused. In two additional studies in both of the dogs iodipamide was infused at 1.0 μmol/min/kg and 3.0 μmol/min/kg, respectively. Lines were fitted to the data by the method of least squares. (No Iod, $r = 0.87$; Iod-1, $r = 0.91$; Iod-3, $r = 0.95$)

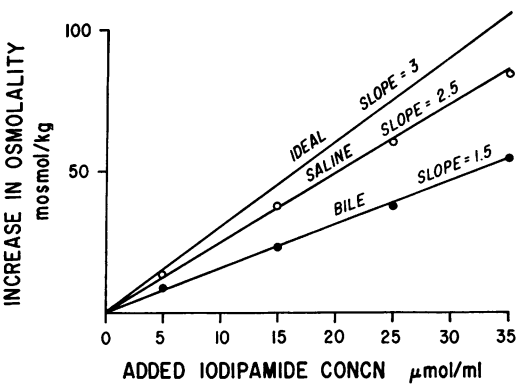

FIGURE 4 The relation between increase in osmolality and the added concentration of iodipamide. The line labeled "ideal" is the predicted osmotic activity of an ideally behaving solution of disodium iodipamide. The lines labeled "saline" and "bile" are derived from the measured increase in osmolality produced by adding disodium iodipamide to isotonic sodium chloride and dog bile, respectively.

In vitro experiments

Increase in osmolality of solutions prepared with increasing amounts of disodium iodipamide in bile and in isotonic sodium chloride (*Fig. 4*). The increase in osmolality produced by adding disodium iodipamide to bile containing 75.5 μmol/ml of bile salts was less than that produced by disodium iodipamide in isotonic sodium chloride for all concentrations of iodipamide. The increase in osmolality expected in an "ideal" solution of disodium iodipamide would be 3 mosmol/mmol as indicated by the slope of the line (Fig. 4). The

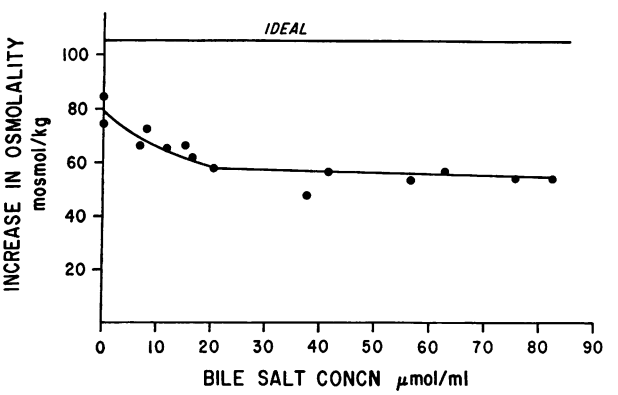

FIGURE 5 The relation between increase in osmolality and bile salt concentration in bile containing a constant concentration of disodium iodipamide. The line labeled "ideal" is the predicted increase in osmolality (105 mosmol/kg) that would be produced by adding disodium iodipamide at a concentration of 35 μmol/ml to bile if it behaved ideally. The curve is the actual measured increase in osmolality and was plotted by eye.

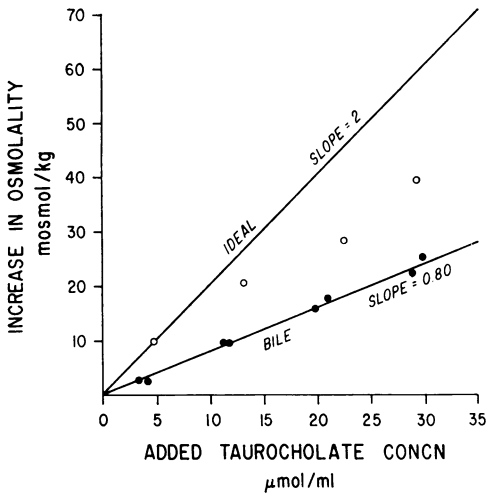

FIGURE 6 The relation between increase in osmolality and the added concentration of sodium taurocholate. The line labeled "ideal" is the predicted osmotic activity of an ideal solution of sodium taurocholate. The line labeled "bile" was derived from the increase in osmolality produced by adding sodium taurocholate to bile. The osmotic activities of sodium taurocholate in isotonic sodium chloride at each concentration studied are represented by the open circles. Each data point has been corrected maximally for contamination due to sodium chloride molecules present in the sodium taurocholate employed in the in vitro studies.

measured increase in osmolality produced by iodipamide in isotonic sodium chloride and in dog bile was linearly related to the concentration of iodipamide. The measured osmotic activity of disodium iodipamide in isotonic sodium chloride was 2.5 mosmol/mmol. In dog bile the osmotic activity of disodium iodipamide was 1.5 mosmol/mmol or only one-half of "ideal."

Increase in osmolality of solutions prepared with a constant concentration of iodipamide in bile containing decreasing concentrations of bile salts (*Fig. 5*). The predicted increase in osmolality of an "ideal" solution of disodium iodipamide at a concentration of 35 μmol/ml would be 105 mosmol/kg as indicated by the line labeled "ideal."

At bile salt concentrations above 20 μmol/ml the measured increase in osmolality was approximately 50 mosmol/kg of solution or about one-half of the "ideal" value. When dog bile was diluted so that the bile salt concentration was below 20 μmol/ml, the increase in osmolality was greater than 50 mosmol/kg but less than in isotonic sodium chloride (indicated by zero bile salt concentration).

Increase in osmolality of solutions prepared with increasing concentrations of sodium taurocholate added to bile and isotonic sodium chloride (*Fig. 6*). The osmotic activity of an "ideal" solution of sodium taurocholate would be 2 mosmol/mmol as indicated by the slope of the line (Fig. 6). When sodium taurocholate was added in increasing concentrations to fresh dog bile there was a linear increase of 1.14 mosmol for each millimole of sodium taurocholate added. This value includes the osmolality contributed by the contaminating sodium and chloride molecules, 0.17 meq of each per millimole of taurocholate. This could account for as much as 0.34 mosmol per millimole of the measured osmotic activity of sodium taurocholate in bile if the osmotic coefficient of sodium chloride is 1.0. Correcting maximally for this contamination the osmotic activity of sodium taurocholate in bile would be 0.80 mosmol/mmol as indicated by the slope of the line labeled "bile." When sodium taurocholate was added to isotonic sodium chloride the increase in osmolality, after correcting for the osmotic effect of the contaminating sodium chloride molecules, was less than ideal at concentrations above 5 μmol/ml as indicated by the open circles.

DISCUSSION

Studies by a number of investigators indicate that bile formation by the liver is the result of two processes (16). Water appears to move by osmotic filtration across the biliary canaliculi (canalicular bile flow) and the bile ducts and ductules (ductular bile flow) (2). Sperber, noting that bile salts are excreted in bile in osmotically significant amounts, was the first to suggest that the hepatic excretion of these compounds may provide the primary osmotic force for the production of canalicular bile (bile salt-dependent canalicular bile flow) (3). That this is not the only mechanism involved in canalicular bile flow is suggested by the fact that in the isolated perfused rat liver, bile flow persists when bile salt excretion is minimal or absent (6). Studies in the rat and rabbit on bile flow and bile salt excretion show that there is a positive intercept for bile flow when bile salt excretion is extrapolated to zero (4). The mechanism by which this bile salt-independent canalicular flow is formed is not known, although it has been suggested that the additional bile flow may be due to stimulation of an active solute pump such as the active transport of electrolytes into bile (4, 5).

It is well established that a number of exogenous organic anions that are excreted by the liver have potent choleretic properties. Hoenig and Preisig showed in dogs that the choleresis due to bromosulfophthalein, ioglycamide, and taurocholate per millimole of compound excreted was 9.2, 11.9, and 7.3 ml, respectively (7). As early as 1953 Langecker, Harwart, and Junkmann noted increased bile flow associated with the biliary excretion of iodipamide in the rat and dog (8). Sperber and Sperber, using data from Fischer's studies

in dogs (10), determined that the excretion of 1 mmol of iodipamide resulted in the production of about 35 ml of bile (17). Their own experiments in rats indicated a choleretic effect of about 25 ml/mmol of iodipamide excreted in bile (17). The results of the present studies show a linear relation between bile flow and iodipamide excretion (Fig. 1). Calculation of the slope of the least squares line fitted to the data indicates that 22 ml of additional bile is formed for each millimole of iodipamide excreted in bile in the dog. The use of steady-state infusions of taurocholate and iodipamide rather than bolus injections, and the collection of bile samples via a cannula rather than a T-tube may explain the difference between the results of the present experiments compared to those of Fischer's.

To determine if the choleresis produced by iodipamide is due to stimulation of canalicular or ductular bile production, erythritol clearance from plasma to bile was studied. Erythritol is an inert molecule which is thought to be completely permeable to the canalicular membrane and is not secreted or reabsorbed by the bile ductules (2). Its clearance from plasma to bile is therefore a convenient measure of canalicular bile flow. In the present studies erythritol clearance was linearly related to the excretion rate of iodipamide and was increased 24 ml/min for each millimole per minute increment in iodipamide excretion rate (Fig. 2). This suggests that the choleretic effect of iodipamide is due to filtration of water across the canalicular membrane (canalicular bile flow).

Sodium taurocholate, which is thought to stimulate canalicular bile flow by virtue of its osmotic activity in bile, had a choleretic potency of approximately 7.8 ml/mmol in the present studies. Data from in vitro studies suggest that when sodium taurocholate is added to bile the osmolality is increased approximately 0.80 mosmol/mmol (Fig. 6). This increase in osmolality is somewhat less than when sodium taurocholate is added to isotonic sodium chloride and almost one-half of that which would be predicted if sodium taurocholate behaved "ideally." It is likely that the osmotic activity of sodium taurocholate is almost one-half of ideal because the taurocholate anion is virtually inactive osmotically due to formation of mixed micelles in bile (16). The osmotic coefficient of sodium taurocholate in bile as measured in the present studies is 0.40 (milliosmoles per liter divided by the concentration in millimoles per liter and the number of ions per formula weight). In isotonic sodium chloride the osmotic coefficient of sodium taurocholate when 30 μmol/ml were added is approximately 0.60. This is similar to the osmotic coefficient of sodium glycocholate at a concentration of 50 μmol/ml (0.60) in distilled water as reported by Moore and Dietschy with freezing-point depression osmometry (9).

Iodipamide is a relatively strong divalent acid, so that if it were completely dissociated in bile, its sodium salt ideally would have an osmotic activity of 3 mosmol/mmol (Fig. 4). Iodipamide's choleretic potency of 22 ml/mmol of iodipamide excreted is approximately 3 times that of taurocholate (7.8 ml/mmol). If the osmotic behavior of iodipamide in bile were similar to that in saline (2.5 mosmol/mmol), it would seem that this difference could be explained entirely by the osmotic effect of iodipamide, since its osmotic activity in bile would be approximately 3 times that of taurocholate (0.80 mosmol/mmol). However, the measured increase in osmolality produced by adding disodium iodipamide in varying concentrations to dog bile (Fig. 4) and adding disodium iodipamide to varying dilutions of dog bile (Fig. 5) was about 1.5 mosmol/mmol. When dog bile was diluted so that the bile salt concentration was below 20 μmol/ml the osmotic activity of iodipamide was greater than 1.5 mosmol/mmol but less than in isotonic sodium chloride. (The bile salt concentrations in bile in in vivo studies were nearly always greater than 15 μmol/ml). A reasonable explanation for the decreased osmotic activity of iodipamide in bile compared with "ideal" and as measured in isotonic sodium chloride is that iodipamide is also incorporated into mixed micelles in bile. Therefore, the osmotic activity of disodium iodipamide in bile is about twice as great as the osmotic activity of sodium taurocholate in bile. This is clearly less than the threefold difference in choleretic potency of iodipamide compared with taurocholate observed in the present in vivo studies.

It must be taken into consideration that even in the case of taurocholate choleresis more water enters the bile than would be osmotically associated with sodium taurocholate itself and that the additional water and solute my enter by a process similar to solvent drag (18). Bile is approximately iso-osmotic, 0.3 mosmol/ml, over varying degrees of choleresis produced by either iodipamide (Table I) or taurocholate (12). If 1 mmol of sodium taurocholate (which has an osmotic activity of 0.8 mosmol in vitro) were excreted without other solute it should be accompanied by 2.67 ml of water (0.8 mosmol divided by 0.3 mosmol/ml) rather than 7.8 ml of water. Likewise, 1 mmol of iodipamide has an osmotic activity of 1.5 mosmol in vitro and should be accompanied by 5 ml of water rather than the observed 22 ml. However, the excess water flow associated with iodipamide excretion (17 ml/mmol, observed flow minus the expected flow) is considerably greater than that associated with taurocholate excretion (5.13 ml/mmol).

Thus is appears that per unit of effective osmotic solute secreted, iodipamide carries appreciably more water and diffusible solute into the bile canaliculi than does taurocholate. The reason for this difference is not apparent but possible reasons might include stimulation of active inorganic solute transport by iodipamide, alteration of canalicular membrane permeability by iodipamide, differences in electrical potential associated with transport of iodipamide and taurocholate, delayed reduction in the osmotic activity of iodipamide, and differences between the spatial distribution of the canalicular secretion of iodipamide and taurocholate.

It is possible that iodipamide may stimulate an active inorganic solute pump which transports solute (e.g., sodium) into the canaliculi and thereby creates an additional driving force for the movement of more water and diffusible solute into the bile (bile salt-independent canalicular flow). This has been suggested as the mechanism responsible for the choleretic potency of SC2644 in the dog and for its prolonged effect on bile flow (19). In the case of iodipamide, one would have to postulate that the effect is directly proportional to iodipamide excretion rate in order to explain the linear relationship between bile flow and excretion rate, a possible but perhaps fortuitous mode of pharmacological action (Fig. 1).

Alteration of canalicular permeability might permit larger quantities of permeant solute and hence larger amounts of water to be carried passively into the bile per osmotic unit of active solute secreted. However such an effect of iodipamide appears to have been excluded by the fact that the choleretic potency of taurocholate is unaffected by simultaneous iodipamide infusion (Fig. 3).

The transport of the divalent anion iodipamide might possibly be associated with the generation of an electical potential gradient across the canalicular membrane which was different from that associated with taurocholate secretion. If so, this might have a distinctly different effect upon the passive movement of other charged solutes (e.g., NaCl) and therefore upon the amount of "extra" water entering the bile per milliosmole of active anion secretion. Unfortunately there is no way to test this possibility at the present time.

If iodipamide were excreted across the canalicular membrane in an osmotically active form comparable to that shown by the line labeled "saline" in Fig. 4, then it might carry additional water and solutes into the canaliculi before losing osmotic activity by incorporation into micelles (as illustrated by the line labeled "bile"). In this case however, the bile should have been distinctly hypotonic, whereas no reduction in osmolality was observed (Table I).

Another possibility is related to probable differences in the canalicular areas devoted to taurocholate as opposed to iodipamide excretion. The extraction of taurocholate during a single passage through the liver is greater than 90% and often close to 100% (20). Thus at rates of secretion less than the transport maximum most taurocholate secretion must involve only those canaliculi at the periphery of the liver lobule. In the case of iodipamide, the extraction of which is appreciably less efficient, the centrolobular canaliculi must also participate in the secretion process.[9] If the permeability of the centrolobular canaliculi for passively moving solutes in water were greater than that of the peripheral canaliculi then one might expect larger quantities of passive solute in water movement during iodipamide than during taurocholate secretion. If this were the case, however, then one would also expect some augmentation of the choleretic potency of taurocholate itself at very high rates of taurocholate secretion where the peripheral canaliculi could be assumed to have been saturated. The limited data which are available at high rates of taurocholate secretion do not appear to suggest that this is the case (12).

It is apparent that the current understanding of the mechanisms of bile production does not permit precise delineation of processes involved in stimulation of canalicular bile flow. In the case of iodipamide, this is of importance since the choleresis produced by iodipamide reduces the maximum concentration of iodine obtainable in bile and limits the degree of radiographic visualization during intravenous cholangiography.

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